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# INJECTIONS OF HOMOLOGOUS STREPTOCOCCI KILLED BY GALACTOSE IN THE TREATMENT OF SUPPURATIVE COMPLICATIONS OF CONTAGIOUS DISEASES.\*

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EVER since the treatment of infections by the injection of dead bacteria was first urged by Wright, interest in this method has been great, but the early reports of brilliant results have not met uniform confirmation. There is on record, however, a sufficiently large number of cases in which good results have followed the use of bacterial inoculations to justify further study of this subject, altho the number of cases in which the most careful use of these methods has failed to produce good results suggests the possibility that in a certain number of instances the good results obtained were merely coincident. Under such circumstances, the careful study of a few cases would seem to be of more value than the routine treatment of a larger number, since there are a great many factors in each case, an inadequate appreciation of which might easily lead to unjustifiable conclusions.

Levy, Blumenthal, and Marxer<sup>1</sup> killed tubercle, typhoid, and glanders bacilli with chemically indifferent agents, such as sugars, glycerin, and urea, and found that considerable quantities of such dead culture could be injected into animals without unpleasant results, and that the injections were followed by marked immunity for the corresponding living bacteria. Weaver and Tunncliffe,<sup>2</sup> in this laboratory, studied the difference in the degree of immunization against living streptococci induced in rabbits by injections of streptococci killed by heat, and by suspension in 25 per cent solution of galactose at 35° C. They tested the immunity by injecting living cultures and by determining the opsonic index. They found that whereas the injection of heat-killed streptococci produced little if any increase in the opsonin, and failed to protect the animals against

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<sup>1</sup> *Centralbl. f. Bakt.*, Abt. I, Orig., 1906, 42, p. 265.

<sup>2</sup> *Jour. Infect. Dis.*, 1908, 5, p. 589.

subsequent injections of living streptococci, or even made them more susceptible, similar injections of galactose-killed streptococci produced a substantial increase in the amount of opsonin, and rendered the animals more resistant than the controls to subsequent injections of homologous living streptococci. They also report two cases of chronic streptococcus infection, one of post-scarlatinal mastoiditis and otitis media and one of chronic erysipelas with acute exacerbations, both of which recovered while under treatment with galactose-killed homologous streptococci.

In a former series of cases Dr. Weaver and I studied the effect of injections of heterologous galactose-killed streptococci in scarlatina and in erysipelas, with reference to their power (*a*) to prevent suppurative complications or to ameliorate the course of the disease when injected during the acute stage of the disease, and (*b*) to modify the course of suppurative complications when administered later. Injections were given in 128 cases, and the following conclusions were reached:

1. The injection of polyvalent, heterologous streptococci, killed by chemically indifferent agents, during the acute stage of erysipelas, has no appreciable effect on the course of the disease. In cases running a prolonged course, such injections appear to exert a favorable influence.

2. The injection of such streptococci during the early stages of scarlet fever does not prevent the later development of local streptococcus complications, altho they may appear a little later in the disease.

3. The injection of such killed streptococci in scarlatina, after local streptococcus complications have developed, exerts considerable influence in hastening recovery. The later the complications appear, and the more chronic the complications are at the time of the injections, the better are the results following the injections. Of nine cases injected during the first week of the fever, only one showed prompt improvement, while of 23 cases injected later, 10 (44 per cent) showed prompt improvement.

4. Homologous streptococci are probably preferable for preparing the material for injection both in protracted, chronic, and recurrent cases of erysipelas, and in cases of scarlatina with local streptococcus complications.<sup>1</sup>

In order to study this matter further, careful observations were made on a new series of cases, comprising two cases of erysipelas, one recurrent, and one recurrent and relapsing, and 12 cases of scarlatina, of which five were complicated by diphtheria, two by measles, and one by measles, diphtheria, and chicken-pox. The cases were studied in the contagious ward of the Cook County Hos-

<sup>1</sup> Weaver and Boughton, *Jour. Infect. Dis.*, 1908, 5, p. 608.

pital, and grateful acknowledgment is hereby made to Dr. Weaver, Dr. Baum, and Dr. Cameron for the opportunity. Swabs were taken from the discharges in each case, and plated on blood agar. Only those cases were used which showed a preponderance of streptococci in the discharge. Subcultures were made on blood-agar slants by inoculating from several typical hemolytic colonies on each plate, grown in the incubator for 24 hours, and washed off with 25 per cent solution of galactose, in which they were suspended for 48 to 72 hours in the incubator (until subcultures proved sterile), separated by centrifugation, and dried in vacuo over calcium chloride at room temperature. Appropriate doses were then suspended in normal salt solution, and injected hypodermically. Only those cases were selected which, judging from our previous experience, were "favorable," that is, cases in which a suppurative complication had become chronic, and the acute stage of the disease had passed, or cases that were distinctly septic. The probable reason that acute infections so seldom show a favorable reaction to bacterial inoculations is that the body is already overtaxed in the production of antibodies, but in my experience "septic" cases seem to constitute an exception to this rule.

Weaver and Tunnicliff found that the maximum increase in opsonin produced in rabbits by an injection of galactose-killed streptococci is obtained on about the third or fourth day. Clinical observations accord closely with this view, altho I have occasionally observed cases in which improvement was noted as early as the next day after an injection. Furthermore, it is generally held that a second dose of dead bacteria rarely produces good results if given before the effects of the first have worn off, which usually means from 5 to 10 days, but cases have been reported in which a small daily dose over a period of one to two weeks is declared to be the cause of an eventual recovery.

In this series only those cases are considered as benefited which showed a sudden, marked improvement within four or five days after an inoculation. In a few cases in which two or more injections were given, it was particularly hard to judge the effect of treatment, as almost any rational method of treatment would surely show some improvement in two weeks' time. It was also noticed that in the

cases of scarlatina there was a marked tendency for suppurative complications to disappear about the sixth week of the disease, whether treated with inoculations or not. There is still another factor tending to confuse results. The cases reported in this series represent only about one-third of the cases for which material was prepared, the other two-thirds during the interval of 6 to 10 days required to prepare the streptococci by this method having either recovered completely, or improved to such an extent that it was not thought advisable to inject them. If this entire series of cases (all of them well marked cases) had been inoculated with "stock vaccines" when first seen, even if the doses had not produced any effect whatever, there would have been at least 67 per cent of good results that might have been attributed to the inoculations; adding the good results obtained in the 14 cases in this series the value of inoculation would be set much too high when the real facts are considered. The cases in this series are, then, a selected group which by comparison were refractory. Because of the various and confusing factors, great care must be taken in observing the cases if the results obtained are to be interpreted correctly.

The opsonic index was not determined systematically in all of the cases, because, after all, the clinical condition is the best criterion, opsonin being only one of the many antibodies produced in the course of an infection. The opsonic index, especially in long-standing suppurations, will often show considerable fluctuations which seem independent of the clinical condition. Moreover, it is questionable if the opsonic index obtained by using a laboratory strain of a bacterium is any index of the patient's resistance to a strain of the same bacterium which is virulent for him. Many observers have noted that the index is often higher for a virulent strain than for an avirulent strain of the same bacterium. This was observed in Case 4 of this series, the only one in which it was looked for.

The doses used in this series ranged usually from 50,000,000 to 500,000,000 cocci (tho once a dose of 10,000,000 was given, but without apparent effect). It is impossible to judge in such a small series of cases as to what the ideal dose would be, especially as there seem to be great individual variations. There seems to be no question that large doses may do harm. I have never observed any

harmful results to come from a single dose of 500,000,000 cocci, tho when such a dose was repeated in a week or so, I have sometimes thought that bad results occurred. I have obtained apparent good results three times with as small a dose as 50,000,000 cocci, but in none of the cases were the results permanent until subsequent larger doses had been given. With a single or an initial dose of 100,000,000 cocci the effects were more lasting. I have obtained good results with a single dose of 500,000,000 cocci, but such a large dose should not be repeated in less than two weeks, and possibly does no more good than a smaller dose. When an initial dose has produced good results, a second dose has not been observed to produce good results unless it is considerably larger than the first (three or four times as large), tho if the first dose has had no effect, a smaller increase will often be efficacious. Probably about 100,000,000 cocci (galactose-killed) is the best routine dose, for this dose is not large enough to produce any bad results, and yet is so small that it may be followed by a large dose if necessary without the risk of bad results. In two cases (3 and 4) it was observed that the first two doses produced good results, but that the subsequent doses, no matter what the size or the interval, were without apparent effect.

**Case 1.**—Girl, six years old, admitted September 6, 1908, sick three days. Scarletina.

September 15. Both ears discharging freely.

September 28. Suppurating cervical gland opened.

October 26. Right mastoid opened, small amount of pus evacuated, and drainage established.

November 10. Ear and wound discharging freely. Opsonic index 1.4. Injected 500,000,000 own streptococci, galactose-killed.

November 11. Discharge increased, moderate local reaction. Opsonic index 3.9.

November 12. Discharge unchanged. Opsonic index 4.8.

November 13. Discharge less. Opsonic index 3.5.

November 14. Opsonic index 1.8. Injected 500,000,000 own streptococci.

November 15. Ver, slight local reaction.

November 16. Discharge remains moderate. Opsonic index 0.4.

November 17. " unchanged. Opsonic index 1.5.

November 18. " " " " 0.9.

November 19. " decreased. " " 4.9.

November 20. " increased. " " 1.0.

November 21. " unchanged. " " 0.8.

November 22. Symptoms developing in other mastoid; taken from hospital.

**RESULT.**—Probably the prolonged negative phase following the second large

injection made matters worse, altho the first injection seems to have produced good results.

**Case 2.**—Woman, 23 years old, admitted November 29, 1908, sick nine days. Scarletina and diphtheria.

December 3. Right ear discharging.

December 22. Discharge profuse. Opsonic index 1.07. Injected 100,000,000 own streptococci.

December 23. Opsonic index 0.84.

December 24. Discharge stopped. Injected 100,000,000 own streptococci.

December 26. Opsonic index 1.8.

December 30. “ “ 1.82.

January 5, 1909. “ “ 2.66.

**RESULT.**—The inoculation apparently produced prompt and marked improvement. The opsonic index remained high so long as the patient was under observation.

**Case 3.**—Boy, 17 years old, admitted December 1, 1908. Diagnosis: Recurrent erysipelas with chronic nasal discharge and chronically enlarged and indurated upper lip.

First attack of erysipelas occurred in December 1907, lasted two weeks, and was of the usual facial type. When the erysipelas subsided, the upper lip remained swollen, and has remained so ever since. He had several attacks of erysipelas, but does not know how many, between December 1907 and July 1908, and each time the lip got worse during the attack, but subsided somewhat afterward, tho it never regained normal size. From July to December 1908 he was free from erysipelas, but the lip remained swollen and the nose remained sore and continued discharging. Another attack of erysipelas occurred December 1, 1908, which subsided in about one week. When first seen, December 18, the lip was swollen to about twice the normal size, a thin muco-sanguino-purulent nasal discharge was present, and the patient complained of constant soreness in the nose. Cultures made from the nasal discharge gave a practically pure growth of hemolytic streptococci. The patient received two injections of 100,000,000 streptococci each (December 29, 1908, and January 4, 1909), and nine days after the last injection he left the hospital.

The patient stated that he felt very much better for a few days after each injection, and two days after the first injection the soreness left his nose, and did not return. The amount of nasal discharge became less after the first injection, but was increased again a few days after the second. The lip became noticeably smaller about four days after the first injection, and continued to decrease in size while under observation. A very marked local reaction followed each injection, and what was apparently a sterile abscess formed at the site of the injection. Altho a complete recovery was not effected, the inoculation apparently exerted a very favorable influence, producing a marked improvement both in the local and in the general condition. The opsonic index determined daily during this period rose after the first injection from 0.84 to 2.75.

After the second injection the index rose to 4.7, but soon fell to about normal. On one occasion (January 5, 1909) it was observed that the opsonic index when determined with the patient's own leukocytes (1.21) was lower than when determined with normal leukocytes (2.04). One month later, when he was much improved, both serum and leukocytes were normal. This same phenomenon was observed in the next case and was now studied more carefully, the observations being reported in detail elsewhere. The leukocyte count varied between 8,800 and 14,750, averaging about 12,000, the

fluctuations following to a certain extent the fluctuations of the opsonic index, tho the correspondence was not close.

One week after leaving the hospital (January 21, 1909) he returned with a mild recurrence of the erysipelas. And it must be noted that in the five cases of recurrent erysipelas, inoculation of homologous or heterologous streptococci, tho often producing good results, never absolutely prevented recurrences. As soon as the acute symptoms had subsided, bacterial inoculations were resumed tho they seemed not to influence the local condition. During the month that he was in the hospital during and after this attack, he received five injections (increasing from 10,000,000 to 200,000,000), and three days after receiving the last one, he left the hospital. Every injection produced a severe local reaction, but the larger doses produced no more reaction than the smaller ones.

**RESULT.**—The first two injections apparently produced marked and permanent improvement. During his second stay in the hospital, he did not react nearly so well to injections, and altho he showed some improvement, it is doubtful if this can properly be ascribed to the inoculation.

**Case 4.**—Man, 32 years old, admitted December 10, 1908. Diagnosis: Recurrent relapsing erysipelas, otitis media. This case is reported in detail elsewhere, especial study having been made of the peculiar reactions which the patient's leukocytes showed in his own and in foreign sera in regard to phagocytosis. His first attack of erysipelas occurred in April 1908, the second in October 1908. Soon after this the left ear began to discharge, and continued to discharge until a couple of weeks before his death. The third attack occurred in December 1908, when he first came under observation. Subsequently he had three recurrences and four relapses. The attacks were all facial, and all except the first migrated down the back. The patient remained in the hospital until his death (May 20, 1909). He received six injections increasing from 50,000,000 to 500,000,000 cocci. The first two injections seemed to produce a favorable influence on both the local and the general condition, but the subsequent injections apparently produced no effect whatever. The injections did not prevent recurrences. The opsonic index following the first two injections rose from 0.36 to 2.5, but soon fell to about normal, and subsequently was not much influenced by the inoculations. Later in the disease the index remained constantly low (0.095 to 0.6). It was repeatedly observed that the index was lower when determined with the patient's leukocytes than when normal leukocytes were used. This was evidently dependent on some reaction between the patient's own leukocytes and serum, for the patient's leukocytes were practically normal when in normal serum, but much less active when in his own serum. It was observed, further, that the addition of a small amount of normal serum (human or horse) would greatly increase the activity of the patient's leukocytes when in his own serum, but when 10 c.c. of fresh normal horse serum was injected, a recurrence of the erysipelas was provoked. It was observed also that the index was higher for the homologous organism, grown under conditions calculated to preserve its virulence, than for a laboratory strain of the same organism, and while the addition of a small amount of normal serum would raise the index for the laboratory strain, it had the opposite effect for the virulent strain. The leukocyte count showed great variations which could not be related to the inoculation, to the opsonic index, or to the clinical course of the disease.

**RESULT.**—In this case the inoculation was apparently without marked or lasting effect; it cannot be said, however, that it produced any bad effects.



**Case 5.**—Girl, eight years old, admitted December 22, 1908. Scarlatina and diphtheria.

January 8, 1909. Ears discharging. Nephritis.

January 15. Measles.

February 12. Both ears and nose discharging freely. Opsonic index 0.72.

Injected 100,000,000 own streptococci.

February 13. Slight local reaction. Opsonic index 1.1.

February 15. Discharge much diminished. General condition much improved, local reaction nearly subsided. Opsonic index 1.02.

February 16. Discharge slight. Opsonic index 0.8.

February 18. Opsonic index 0.67. Injected 100,000,000 own streptococci.

February 19. Opsonic index 1.26.

February 22. Discharge present but slight.

February 24. Chicken-pox. Injected 200,000,000 own streptococci.

February 26. Discharge much increased.

March 2. Discharge slight.

March 6. Moderate amount of bloody discharge. Injected 400,000,000 own streptococci.

March 8. Discharge much reduced. Great improvement in general condition.

March 10. Discharge remains about the same. Opsonic index 0.84.

March 11. Taken home.

**RESULT.**—In this case three of the four injections given apparently produced good results, but the intercurrent infection of chicken-pox interfered markedly with the course of the disease, and with the interpretation of the results.

**Case 6.**—Boy, six years old, admitted January 15, 1909. Scarlatina.

February 26. Measles.

March 10. Ear discharging freely.

March 30. Injected 500,000,000 own streptococci.

April 8. Discharge still present.

April 10. Discharge very slight—taken home.

**RESULT.**—The improvement in this case, occurring 11 days after the inoculation, cannot be attributed with any certainty to its effect.

**Case 7.**—Boy, six years old, admitted March 4, 1909. Scarlatina and diphtheria.

March 15. Ear discharging.

March 30. Ear discharge unchanged; injected 500,000,000 own streptococci.

April 1. Moderate local reaction. Discharge the same.

April 8. Discharge slight.

April 12. Discharge stopped.

**RESULT.**—The improvement in this case occurred so late as not to be fairly attributable to the inoculation.

**Case 8.**—Girl, eight years old, admitted February 23, 1909. Scarlatina.

March 1. Ear discharging.

March 30. Discharge continues. Injected 500,000,000 own streptococci.

April 1. Moderate local reaction, discharge slightly increased.

April 2. Discharge diminished.

April 3. Discharge stopped.

**RESULT.**—Inoculation apparently produced prompt and marked improvement.

**Case 9.**—Girl, five years old, admitted March 15, 1909. Scarlatina and diphtheria.

March 20. Nose and ears discharging freely.

March 30. Discharge continues; "septic"—seems moribund. Injected 100,000,000 own streptococci.

March 31. Died.

RESULT.—This case is included in the series for the sake of completeness. It cannot be said that any effect whatever was produced in this case by the inoculation.

**Case 10.**—Boy, 15 months old, admitted March 17, 1909. Scarletina and diphtheria.

March 21. Aural discharge, soon becoming profuse.

April 24. Ears and nose discharging profusely. General condition very poor—semi-stuporous. Injected 50,000,000 own streptococci.

April 28. Marked improvement in general condition.

May 4. General condition again poor—looks moribund. Injected 50,000,000 own streptococci.

May 5. Condition somewhat better—removed from hospital. Further details of illness not available except that child recovered.

RESULT.—Inoculation apparently produced prompt and marked improvement in general condition.

**Case 11.**—Boy, three years old, admitted March 18, 1909. Diphtheria.

March 23. Scarletina, moderate severity.

April 2. Both ears discharging.

May 4. Measles, moderate severity.

May 21. Discharge still continues. Injected 100 000,000 own streptococci.

May 26. Taken from hospital, discharge still profuse.

RESULT.—Inoculation apparently produced no result.

**Case 12.**—Girl, three years old, admitted May 15, 1909. Scarletina.

May 29. Diphtheria.

May 31. Ear discharging.

June 6. Cervical abscess opened.

June 20. Ear discharge ceased, neck still discharging. Injected 100,000,000 own streptococci.

July 2. Neck discharge ceased, another small abscess on neck opened, which ceased discharging in a few days.

RESULT.—Inoculation apparently produced no effect.

**Case 13.**—Boy, six years old, admitted July 8, 1909. Convalescent scarlatina (fifth week?), suppurative otitis media, subacute mastoiditis, suppurative cervical adenitis.

July 27. Profuse discharge from both ears and from wound in neck. General condition poor. Injected 50,000,000 own streptococci.

July 29. Marked improvement in local and general condition. From this time until date of dismissal the general condition continued to improve. The purulent discharge still continued tho much less in amount.

August 1. Cervical abscess healed.

August 4. Injected 100,000,000 own streptococci.

August 9. No appreciable result from last injection. Injected 200,000,000 own streptococci.

August 12. Aural discharge much diminished.

August 14. Aural discharge ceased.

RESULT.—Injections apparently produced prompt and marked improvement.

**Case 14.**—Boy, eight years old, admitted July 12, 1909. Diagnosis: Scarlatina, epilepsy.

July 15. Profuse discharge from nose and from both ears.

July 27. Discharge still profuse. Injected 50,000,000 own streptococci.

July 30. General condition much improved. Local condition unchanged.

August 4. Condition same. Injected 100,000,000 own streptococci.

August 9. Discharge somewhat less. Injected 250,000,000 own streptococci.

August 10. Discharge much improved.

August 14. Discharge ceased.

RESULT.—Injections apparently produced prompt and marked improvement.

Of these 14 cases, eight recovered completely while under observation, but in only five was the recovery due, apparently, to the inoculation. In the other three, the aural discharge diminished gradually, and finally stopped completely about 12 days after the inoculation, but in the absence of any sudden and well marked improvement, it is better to consider them conservatively. Of the six cases which did not recover completely while under observation, only two failed to show improvement and one of these died the day after the inoculation, so that perhaps it is not fair to place any stress on this one. Of the entire 14 cases, nine showed improvement following the injections, and five did not show improvement which could be ascribed to the injection; but of the five, three recovered under observation, one died the day after the injection, and one was taken from the hospital a few days after the injection, while the discharge was still profuse; of the nine which showed improvement, one (Case 1) later became worse, apparently because of two large injections at a short interval; one (Case 4) died four months later, the course of the disease during the latter part of the sickness being apparently uninfluenced, favorably or unfavorably, by the inoculation; one (Case 3) showed marked improvement after the first two injections and later, altho he continued to improve, the improvement was very slow and not plainly due to the inoculation; and in one (Case 12), altho the improvement was quite marked early, the course was much disturbed by an intercurrent infection of chicken-pox, which, in several cases in our experience, has invariably had the effect of making an aural discharge much more profuse and more resistant to treatment.

In the entire series of 14 cases, then, which may be considered as

more refractory than the average of cases of this class, we may fairly claim, as due directly to the inoculation, 36 per cent cured, 28 per cent improved, while 36 per cent were uninfluenced by the treatment. No ready explanation is at hand why some of the cases should respond to early treatment, but not to later treatment, altho they may go on to recovery, but apparently not influenced by the injections. On the other hand, some cases will not respond to the first or second injection, but will respond to later injections. In view of the generally accepted fact that acute infections, especially suppurations, do not usually respond well to bacterial inoculations, the behavior of cases of sepsis is without ready explanation, unless they be ascribed to error or coincidence, which seems not to be reasonable. In seven cases (three in this series, and four reported previously) in which injections were given in the presence of marked evidence of sepsis, prompt improvement (in one to three days) was noted in all but one, and that one was moribund when injected; another case that seemed moribund when injected showed a marked improvement the next day. In other cases in which the condition was not so marked, the patients would often declare that they felt much better after an injection, and the improvement was certainly not altogether psychic. This improvement in general condition was often noted to precede improvement in the local suppurative process by a day or two, and was sometimes present even when no change in the local condition could be detected. From purely anatomical considerations it is easy to see why a long-standing purulent discharge, especially one involving a bony cavity, as a mastoiditis or an otitis media, could not be expected to stop at once, no matter how much the bodily resistance might be raised.

#### CONCLUSIONS.

The injection of homologous galactose-killed streptococci in local streptococcus complications of scarlatina and of erysipelas in many cases appears to have a marked effect in hastening recovery. This series of 14 rather refractory cases shows 36 per cent of recoveries, and 28 per cent of improvements, due, apparently; directly to the inoculations. The average initial routine dose should be about 100,000,000 cocci. Large doses, especially if repeated at short intervals, are capable of producing harmful results.

The injection of small doses (50,000,000) of galactose-killed homologous streptococci appears to exert a favorable influence on septic conditions complicating scarlatina.

Some cases of streptococcus infection may show favorable results following a few early injections, when later injections appear to produce no reaction whatever.